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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,228	06/08/2005	Gustave Bergnes	P51400	9235

20462 7590 03/30/2006

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EXAMINER	
KIFLE, BRUCK	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 03/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/538,228	BERGNES ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,22,24,27,28,30,31,33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,22,24,27,28,30,31,33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/08/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claim Rejections - 35 USC § 112

Claims 1-3, 6, 22, 24, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) The term "substituted" without saying which substituents are intended is indefinite. One skilled in the art cannot say which substituents are permitted and which ones are not.

ii) The term "heteroaryl" is indefinite because it is not known how many atoms are present, how many and what kind of heteroatoms are involved, what size ring is intended and how many rings are present.

iii) The term "carbocyclic" is indefinite because it is not known what kind of a ring is intended (monocyclic? Bicyclic? Spiro? Fused? Bridged? Saturated? Unsaturated?).

iv) The phrase "pharmaceutically acceptable derivatives" is indefinite because one skilled in the art cannot say what derivative is intended.

v) The nature of the additional ingredients in claim 28 is not known.

Note that compounds, corresponding compositions, a method of use and a process of making that are of the same scope are considered to form a single inventive concept under PCT Rule 13.1, 37 CFR 1.475(d). Claims 1 and 28 are not so linked as to form a single inventive concept.

Claims 1-3, 6, 22, 24, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical salt, does not reasonably provide enablement for solvates of the compound of formula I. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Applicants have not shown how one skilled in the art can arrive at a given solvate. None of the compounds made are crystallized out as solvates. Arriving at a given solvate is not routine experimentation because it is unpredictable. One cannot make any solvate or hydrate of a compound.

Claims 1-3, 6, 22, 27, 28, 30, 31, 33 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of claim 24, does not reasonably provide enablement for using the compounds of claim 2. The specification is not adequately enabled for the scope of fused rings that have diverse atoms at A, B, D and E and differing ring systems fused to the pyrimidinone. Compounds made and tested represent the scope of claim 24, not claim 2. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.
a) Determining if any particular claimed compounds with the different ring heteroatoms and multitudes of substituents would be active would require synthesis of the substrate and subjecting it to testing with Applicants' ATPase assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in Scheme 3a, page 43, which merely states Applicants intent to make and use such compounds. c) In the instant case none of the working examples contains any radical beyond a quinazolinone substituted by chloro at the 7-position, a benzyl at the 3-position and an ethyl or propyl substituted methylene linker linking it to a 1,4-diazepinone. None of these

working examples contain a basic or acidic group. None of these contain electron deficient hetero aromatic rings. There are no multiple bonds either. d) The nature of the invention is inhibition of KSP and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the KSP binding activity of small ligands and the ability of those compounds to inhibit KSP. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. e) The state of the art is detailed knowledge of the receptor is lacking. No X-ray structure of the receptor is known and the structural requirements of ligands to this receptor are poorly understood. The six-membered benzene ring of Applicants' working example quinazolinone compounds is non-basic. The pyridine ring, pyrimidine ring, and the pyrazine ring of the rejected compounds are strongly basic, basic, and weakly basic respectively. The pyridine ring and the pyrazine ring of the rejected compounds are hydrogen bond acceptors. The benzene ring of Applicants working examples is not. The pyridine ring and the pyrazine ring of the rejected compounds are pi-electron deficient. The benzene ring of Applicants working examples is not. There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (II) will all share the same biological properties. For example, the rings include N with extra basic sites. The rings include thiophene with additional polarizable S atoms. The diverse claimed fused heteroaryl rings are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar

compounds will have such activity, *In re Surrey* 151 USPQ 724. Compounds made and tested represent the scope of claim 24.

f) The artisan using Applicants invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of billions of compounds of formula (II). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim would read on KSP inhibition *in vitro*, KSP inhibition in mammals with below normal KSP activity, KSP inhibition in mammals with normal KSP activity, or in asymptomatic mammals with up-regulated KSP activity. The specification fails to teach any benefit to be gained from such actions. Is extensive experimentation required on the part of a potential infringer to determine if his use of Applicants' inhibitor falls within the limitations of applicants' claim? *In re Kirk and Petrow*, 153 USPQ 48 (CCPA 1967). As the Supreme Court said in *Brenner v. Manson*, 148 USPQ at 696: "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." As U.S. Court of Customs and Patent Appeals stated *In re Diedrich* 138 USPQ at 130, quoting with approval from the decision of the board: "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."

Claims 31 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating the diseases embraced by these claims. Claims 31 and 33 are drawn to the treatment of cancer. The specification does not provide enablement for the treatment of cancer generally. No compound has ever been found that can treat cancers generally even though massive efforts have been directed towards this end. Since this assertion is contrary to what is known in oncology, proof must be provided that this revolutionary assertion has merits. Nearly all anticancer drugs are effective against only a limited group of related cancers. Therefore, a compound effective against cancer generally would be a revolutionary exception. Applicant is asserting that he succeeded where others have failed. Where extensive efforts have all failed, it is reasonable for the Patent and Trademark Office to require proof that the claimed invention actually works for this specific utility. It is well established that a utility rejection is proper when scope of enablement is not reasonably correlated to the scope of the claims. (In re Vaeck 20 USPQ2d 1439, 1444, In re Ferens 163 USPQ 609).

In re Buting 163 USPQ 689 establishes that even clinical tests showing that a compound found to be useful in the treatment of two types of cancers was not sufficient for a much broader range.

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally

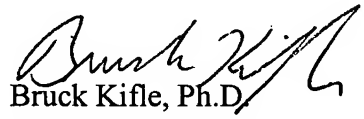
tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 571-272-0668. The examiner can normally be reached Tuesdays to Fridays between 8:30 AM and 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
March 24, 2006